CHAPTER 1

Introduction

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Diabetes Mellitus

In healthy subjects, the concentration of glucose in plasma is remained within a narrow range (3.5-7.0 mmol/l) despite fluctuations in nutritional intake, physical exercise and other (physical or psychological) influences. One of the major determinants of this stable plasma glucose is the action of the blood-glucose lowering hormone insulin.

Insulin secretion consists of 2 components: a continuous low basal rate and short-lived bursts in response to stimuli. Basal insulin secretion occurs in the fasting state to inhibit hepatic glycogenolysis, ketogenesis and gluconeogenesis and accounts for approximately 40% of the total daily insulin output. Insulin secretion on top of basal secretion occurs when plasma glucose level exceeds 4.4-5.6 mmol/l to restore euglycaemia by promoting peripheral glucose uptake and storage. Through these mechanisms, plasma glucose rises to a peak in 30-60 minutes after eating and returns to basal concentrations within 2-3 hours. In healthy individuals, basal insulin secretion together with the reactivity of insulin secretion in response to various stimuli are key factors in ensuring glucose homeostasis, permitting stability and reproducibility of blood glucose [1,2].

Diabetes mellitus refers to a group of metabolic disorders that share the phenotype of hyperglycaemia. This hyperglycaemia results from defects in insulin secretion, insulin action or both. Several distinct types of diabetes mellitus, caused by a complex interaction of genetic and environmental factors, exist. The vast majority of individuals with diabetes mellitus fall into two broad etiopathogenetic categories: type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), accounting for ~5-10% and ~90-95% of all cases, respectively [3]. T2DM is characterized by hyperglycaemia and often combined with insulin resistance, with a relative impairment in insulin secretion. In a minority of T2DM cases, a relative impairment in insulin secretion exists without insulin resistance, while in T1DM there is an absolute impairment of insulin secretion. In this thesis, the focus will be on individuals with T1DM.

Type 1 diabetes mellitus

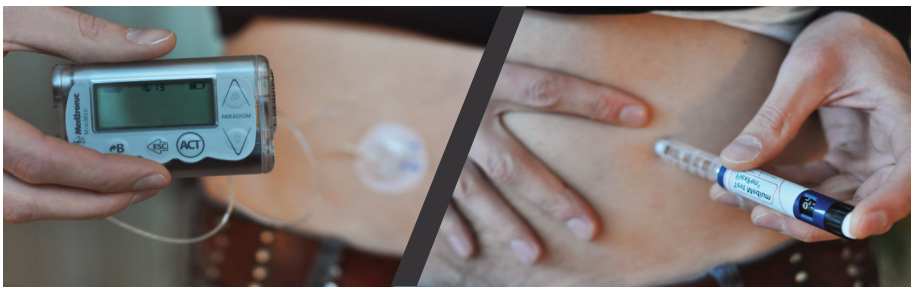
In T1DM there is an (almost) absent secretion of insulin due to various (auto-immune) mechanisms, which would lead without exogenous insulin administration to ketoacidosis and ultimately death [4–6]. T1DM is characterized by hyperglycaemia with the eventual development of micro- and macrovascular complications. In individuals with T1DM,

it has been unambiguously proven that the development of micro- and macrovascular complications amongst others is linked to the duration and severity of hyperglycaemia and can be either prevented or delayed by intensive insulin therapy [7,8]. Therefore, efforts are made to achieve blood glucose levels as close to physiologic as possible while balancing the risk of hypoglycaemia. Apart from lifestyle interventions, e.g. regular exercise, a healthy diet and non-smoking habits, and treatment of associated conditions, e.g. hypertension, dyslipidemia and/or obesity, the mainstay of current T1DM treatment is insulin replacement therapy.

Insulin replacement therapy

An ideal insulin replacement regimen should achieve blood glucose levels as close to the physiological state as possible and thus be able to accurately reproduce both the basal and 'burst' (bolus) component of normal insulin secretion. This is the aim of the two most common insulin replacement modalities in T1DM: multiple daily injections (MDI) of insulin in the subcutaneous (SC) tissue and continuous subcutaneous insulin infusion (CSII) with an externally placed pump (see Figure 1).

FIGURE 1 **Subcutaneous modes of insulin administration: continuous subcutaneous insulin infusion with an externally placed pump (left) and injections of insulin (right).**



In general, the MDI treatment regimen consists of a combination of a basal (intermediate- or long-acting) insulin, injected (mostly) once daily, and a bolus (short-acting) insulin injected with meals, in order to mimic the physiologic insulin profile. For this purpose the insulin analogues, introduced in the late 1980's, are used. Insulin analogues can be subdivided in rapid-acting (insulin lispro, aspart and glusine) and long-acting (insulin glargine, detemir and degludec). These preparations differ from the previously used human

insulin by amino-acid substitutions or addition of myristic acid, leading to changes in their ability to self-associate [9]. Compared to human soluble insulin, insulin analogues are believed to be characterized by less variability in absorption and shorter (or longer for the long-acting analogues) duration of action and thus more rapid onset and less postprandial glucose fluctuations [10,11].

CSII with a portable, externally placed, pump was introduced in the 1970's. The first available device (the Mill Hill infuser) delivered insulin through a subcutaneously placed cannula by a miniature pump, carrying a 2ml syringe, at two rates: a slow basal (47 µl/hour) and an eightfold higher rate [12]. Although the present external insulin pumps are more sophisticated than the initial model, the rationale is identical: insulin is administered at a slow basal rate, 24 hours a day, through a cannula inserted in the SC tissue. Furthermore, patients can administer insulin boosts (boluses).

Compared to MDI, CSII seems to improve glycaemic regulation in adult patients. Although outcomes of individual studies vary, meta-analyses that compared MDI with CSII have reported slightly lower HbA1c levels with CSII, with a mean difference of about 3.3-6.7 mmol/mol (0.3-0.6%), and a similar rate of severe hypoglycaemic events [13–16]. CSII offers patients the use of pre-programmable basal insulin rates, a bolus function (with bolus calculator) and linkage to external devices such as a personal computer or mobile telephone. With these functions, increased flexibility with respect to diabetes management in activities of daily living can also improve treatment satisfaction as compared to MDI [15,17,18].

Drawbacks of SC insulin therapy

With MDI and CSII deviations from the normal response occur due to pharmacokinetic and pharmacodynamic properties of SC administered insulin. For example, the lagtime to insulin action after SC injection varies between 5-15 minutes for the rapid-acting insulin analogues with an effective duration between 4-6 hours [19]. Partly due to tissue properties, and partly due to the tendency of insulin molecules to aggregate, the rate of SC absorption of insulin varies within and between individuals. Factors that contribute to the inconsistent pharmacokinetics of insulin are related to the insulin preparation (volume, concentration, additives), differences between injection sites (anatomical region, depth of injection, degree of fibrosis, injection infiltrates) or changes to the injection site (local blood flow (temperature), other substances applied). These combined factors may lead to a pronounced variability of the appearance of

insulin in the circulation of up to 35% [20]. Furthermore, the variability in insulin sensitivity adds to the variance in absorption and is also a determinant of insulin pharmacodynamics.

As a consequence, SC insulin administration may lead to unpredictable fluctuations in blood glucose concentrations. These fluctuations in themselves are associated with elevated HbA1c levels and hypoglycaemic episodes with subsequent stress, anxiety, impaired well-being and reduced quality of life (QoL). This unpredictability is also illustrated by the fact that, despite all efforts, approximately 15-25% of T1DM patients achieve the recommended HbA1c level of less than 53 mmol/mol (7.0%) and the average patient suffers from two symptomatic hypoglycaemic episodes per week [21,22]. Thus, the current challenge of insulin therapy is to improve glycaemic control with more time in normoglycaemia, without increasing the incidence of hypoglycaemia and a minimal negative impact on QoL, which would eventually translate in a reduction of complications. Despite all efforts of patients and health care providers, in part of the patients this challenge remains difficult to achieve using the SC route of insulin administration. Therefore, alternatives have been developed; one such alternative is continuous intraperitoneal (IP) insulin infusion (CIPII) using an implantable pump.

Continuous intraperitoneal insulin infusion

A BRIEF HISTORY

The first trials with IP insulin infusion were performed in the early 1980's, using externally placed portable pumps connected to a catheter that had the distal end located in the IP space [23–26]. Although the results of these studies demonstrated that IP insulin infusion stabilizes plasma glucose and normalizes plasma free insulin levels, complications associated with the combination of an external pump and an indwelling catheter, such as infections, imposed a tremendous burden. Consequently, CIPII using an implantable pump came into focus.

The first implantable pumps available for daily care were used in the late 1980s for short-term IP insulin treatment. Again, near-normalization of blood glucose profiles without peripheral hyperinsulinaemia was established [27–30]. From three initial investigational models of implantable insulin pumps (Infusaid, model 1000, Strato/Infusaid, Norwood, Ms, USA; Minimed Implantable Pump (MIP) 2001, Minimed Technologies, Sylmar, CA, USA; Siemens ID3, Siemens-Elema, Solna, Sweden), only the MIP 2001 model persisted and succeeded in obtaining the European Community approval in 1994.

However, several problems with the implantable pump system occurred. After some years of reasonable results, a high incidence of insulin underdelivery was detected which was related to modifications of the insulin used in the implanted pump [31]. In order to comply with the European regulations, slight modifications were made in the insulin preparation in 1993 which resulted in impaired chemical stability in the MIP 2001 model. In 1997, this was resolved by the use of a new 21PH ETP insulin variant (U-400 HOE 21PH, semi synthetic human insulin of porcine origin, trade name: Insuplant® Hoechst, Frankfurt, Germany, nowadays Sanofi-Aventis) with improved stability [32]. After changing the insulin there was also a decrease in the number of catheter obstructions due to tissue overgrowth at the catheter tip, which was possibly due to a decrease in immune-inflammatory reactions against insulin deposits in the peritoneal space [28–30,33,34]. The MIP 2001 model was also equipped with a side-port, allowing transcutaneous flushes or rinse procedures (using NaOH) in case of suspected catheter obstructions [31]. Nevertheless, insulin underdelivery still occurred due to the fact that the lumen of the catheter was unable to absorb the forward stroke volume of the pump piston. Modifications of the catheter side-port, in order to accumulate the initial pressure impact, were necessary to overcome this problem. Together, the improvements of the insulin, pump and catheter resulted in a safe and reliable insulin delivery with the MIP 2001 model from 1998 onwards [35]. Another problem that occurred was the increased production of anti-insulin antibodies seen in some patients treated with CIPII [36,37]. Although the exact cause remains unknown, it has been suggested that the increased anti-insulin antibodies concentrations may be due to insulin modifications occurring during storage in the implantable pump or due to the inadvertent formation of insulin aggregates which are known to be more antigenic [38]. These anti-insulin antibodies associate with insulin, in particular post-prandial and can theoretically lead to higher postprandial blood glucose and an increased risk of delayed hypoglycaemia [39]. Nevertheless, this increased immunogenicity did not induce metabolic consequences, change insulin requirements or the number of hypoglycaemic episodes [40]. In addition, the increased anti-insulin antibodies did not seem to correlate with the presence or absence of other autoimmune diseases [41].

Although many issues were resolved and experience with CIPII increased over time, further development was delayed and the widespread use of CIPII was impaired due to persistent concerns regarding safety and cost(-effectiveness).

PHYSIOLOGICAL PROPERTIES

With CIPII, insulin is directly infused in the IP space. Speed of insulin absorption from the peritoneal space depends on injected volume, concentration of insulin solution and duration of injection, but the insulin is to a large extent directly absorbed into the portal system, where

it is detectable within 1 minute after administration [42,43]. Because of the absorption by the portal system there is a higher hepatic uptake of insulin, with the first-passage hepatic insulin extraction being directly after absorption, and an alleviation of peripheral plasma insulin concentrations is reached as compared to SC insulin administration [44–48]. IP administered insulin takes approximately 15 minutes to reach its peak effect and allows blood glucose values to return to baseline values more rapidly with reproducible and more predictable insulin profiles compared with SC injections of insulin [44,49–51]. Thus, the IP route of insulin administration mimics the physiological state more than the SC route. Other possible positive effects of IP insulin infusion include improvement of the impaired glucagon secretion, also during exercise, and enhanced hepatic glucose production in response to hypoglycaemia [47,52–55]. Although the exact mechanisms behind these two phenomena are unknown it has been hypothesized that lower peripheral plasma insulin concentrations with CIPII may (partly) restore glucagon release or that CIPII increases hepatic sensitivity to glucagon or hepatic glucose utilization during hypoglycaemia [47,55].

EFFECTS ON GLYCAEMIC CONTROL

Three randomized studies have compared the effects of CIPII, using an implantable pump, on glycaemic control with SC insulin therapy in patients with T1DM. The main results of these studies are depicted in Table 1. Haardt *et al*. found improvements in both HbA1c and the frequency of hypoglycaemic events during CIPII as compared to MDI treatment [56]. Although Selam *et al*. found a decline of HbA1c levels after 4 months in both the CIPII and SC treatment group, there were no inter-group differences between CIPII or intensive SC treatment [57]. In 2008, a randomized cross-over study performed by Logtenberg *et al*. compared the effects of CIPII and SC insulin in 24 patients with poorly regulated T1DM. Glycaemic control improved with CIPII as compared to SC treatment, with a mean difference in HbA1c of 8.4 mmol/mol (0.76%) in favour of CIPII without an increase in hypoglycaemic events [58].
Several observational studies were in concordance with these results by showing a decrease in HbA1c and a lower incidence of hypoglycaemic events with CIPII treatment [30,34,59–62]. However, it should be mentioned that all of these studies were non-blinded and performed in small and selected T1DM populations.

In addition to HbA1c several studies assessed glycaemic variability, another facet of glycaemic regulation and suggested to help predict hypoglycaemia and diabetes related complications [63,64]. Although performed before the era of rapid-acting insulin analogues and continuous glucose measurement (CGM), these studies demonstrated less glycaemic variability (expressed as the standard deviation of capillary glucose concentration) during CIPII as compared to SC therapy [56,57,62].

TABLE 1 Prospective, randomized studies comparing CIPII with SC (both MDI and CSII) insulin administration in T1DM, concerning HbA1c and hypoglycaemic events.

Study **1st author, year; country**	**Study group** *Patients (% female, diabetes duration, age)*	*Number (I/C)*	**Period (months)**	**Study arm** *Intervention*	*Control*	**Endpoint**	**Results** *Intervention (%)*	*Control (%)*	*Difference intervention vs. control*
Logtenberg, 2009; the Netherlands [a]	54, 23±11 yr, 44±12 yr	24/24	16	CIPII (MiniMed, 2007C)	SC (MDI and CSII)	HbA1c	70 → 58	70 → 70	-8.4 (-15.6, -1.2) [*]
						Hypoglycaemia, Grade 1 [b]	4.0 → 3.5	4.0 → 4.0	-0.5 (-1.2, 0.2)
						Hypoglyacemia, Grade 2 [c]	2.7 → 2.3	2.7 → 2.7	-0.4 (-0.9, 0.04
Selam, 1992; USA	48, NR, 38±3	NR/NR (21 in total)	9	CIPII (Infusaid, model 1000)	SC (MDI and CSII)	HbA1c [f]	80 → 68	70 → 65	NR
						Hypoglycaemia	NR	NR	NR
Haardt, 1994; France [a]	20, 13±10 yr, 39±5 yr	10/10	12	CIPII (Infusaid, model 1000 and MiniMed)	SC (MDI)	HbA1c	59 → 55	64 → 69	NR
						Hypoglycaemia [d]	NR → 5.7	10	NR

[a] Cross-over trial, [b] Number of hypoglycaemic episode <4.0 mmol/mol per week, [c] Number of hypoglycaemic episode <4.0 mmol/mol per week, [d] Hypoglycaemic episodes per month, [e] Defined as the SD of capillary glucose values [f] No exact values mentioned, presented data is extracted from graph. Abbreviations: CIPII, continuous intraperitoneal insulin infusion; SC, subcutaneous; MDI, multiple daily injections; CSII, continuous subcutaneous insulin infusion; T1DM, type 1 diabetes mellitus; NR, not reported; YR; year(s).

EFFECTS ON QUALITY OF LIFE

Apart from glycaemic control, CIPII positively affects QoL. In the cross-over trial by Logtenberg et al. the self-reported general QoL on the SF-36 questionnaire improved significantly during CIPII therapy as compared to SC insulin therapy [65]. Next to QoL, treatment satisfaction also increased with CIPII as compared to SC insulin [65]. An increase in diabetes specific QoL was reported in the randomized trial by Selam *et al*. [29]. Comparable findings were found in a French cross-sectional study in which better treatment satisfaction and less 'diabetes worry' was found [66].

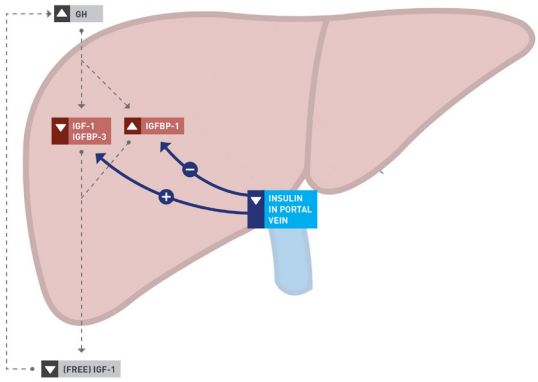
Nevertheless, baseline QoL seems to be rather poor in this group of patients. This is illustrated by a Dutch observational study in which DeVries *et al*. found scores on the subscales 'physical functioning' and 'mental health' of the self-reported general QoL, using the SF-36 questionnaire, among patients using CIPII to be similar to patients with a serious medical condition such as symptomatic chronic heart failure, post myocardial infarction with persistent symptoms, or hypertension with severe heart failure symptomatology or a history of stroke. For the subscales 'general health', 'pain' and 'social functioning' the SF-36 scores even resembled those of persons with a serious chronic medical disorder and current depressive symptoms [67]. In addition, there was a high number of CIPII patients with psychiatric symptoms and scores on the diabetes specific DQOL questionnaire were significantly worse for patients using CIPII as compared to patients with T1DM without CIPII [67].

EFFECTS BEYOND GLYCAEMIC CONTROL

Insulin does not only affects glycaemia but influences a wide range of processes. Because IP insulin is absorbed to a large extent in the portal vein catchment area, the insulin concentration in the portal vein and the peripheral plasma insulin concentrations are more physiological compared to SC administered insulin [44–47]. This has consequences for other endocrine systems, e.g. the growth hormone (GH) - insulin-like growth factor-1 (IGF1) axis. In healthy subjects, circulating IGF1 is synthesized in the liver after stimulation of the GH-receptor and plays a central role in cell metabolism and growth regulation [68–70]. Insulin is suggested to increase the sensitivity of the liver to GH by up regulating GH receptor expression, and thereby augmenting IGF1 production [71]. Insulin also seems to increases IGF1 bioactivity by down regulating hepatic production of the IGF binding protein-1 (IGFBP1) at the transcriptional level [68,72].

In patients with T1DM, low concentrations of total IGF1 and IGFBP3 and high concentrations of IGFBP1 and GH are present probably due to insufficient insulinization of the liver secondary to a lack of endogenous insulin in the portal vein (see Figure 2 for an overview of the suggested

FIGURE 2 **Alterations in GH-IGF1 system in T1DM and suggested role of insulin concentrations in the portal vein.**



The (+) and (-) indicate positive and negative correlations, respectively. The (▲), (▼) and (=) indicate increases, decreases and unaltered concentrations as found in studies towards IP insulin administration, respectively [73,76,78,88–92]. Abbreviations: GH, growth hormone; IGF1, insulin; like growth factor-1, IGFBP-1/-3, insulin like growth factor binding protein -1/-3.

relationships of portal insulin concentrations and the GH-IGF1 axis in T1DM) [73]. Low IGF1 concentrations have been suggested to influence IGF1 sensitive tissues such as the vasculature, bone and muscle and to contribute to increased insulin resistance and an increased risk of long-term diabetes complications [74,75]. Although these abnormalities in the GH-IGF1 axis have been described in situations of poor glycaemic control, SC insulin administration and improvements in glycaemic control only seem to attenuate these disturbances but do not completely reverse them [76–79]. The hypothesis that higher portal insulin concentrations achieved with CIPII could have a beneficial effect on the impaired GH-IGF1 axis has been tested in a few studies. Shishko *et al*. studied the effects of IP insulin infusion among newly diagnosed T1DM patients and observed that IP insulin but not SC insulin therapy normalized IGF1 and IGFBP1 concentrations [80]. However, this study lacked data about endogenous insulin secretion. Among C-peptide negative T1DM patients, a longitudinal study by Hanaire-Broutin *et al*. showed that IGF1 concentrations were higher with CIPII therapy than during prior intensive SC therapy [81]. Furthermore, IGF1 concentrations tended to rise to a to a low-normal level one year after initiating CIPII, despite a lack of improvement in HbA1c. Further evidence for the concept that IP insulin influences the IGF1 was provided by Hedman *et al*. by finding, in addition to higher IGF1 concentrations, increased IGF1 bioactivity during CIPII when compared with CSII among T1DM patients [82]. Further research needs to be performed in a larger population and over a longer period to test the hypothesis that CIPII could alter the dysregulated GH-IGF1 axis in T1DM.

COMPLICATIONS AND COSTS

In one study, 80% of the patient who used CIPII did not experience any pump related complication during a 15-year period. Among the patients that did experience complications, local infection and pain were the most frequent complications [83]. The current average operation free period, ideally 1 procedure every 7 years to replace the pump when the battery has been depleted, was 4.5 years [83]. No CIPII related mortality has ever been reported.
An important issue of CIPII therapy is the high costs. In 1994, Haardt *et al*. estimated the costs of CIPII to be 2.6 fold higher as compared to MDI [56]. In 2010, direct pump- and procedures (such as regular filling and rinsing procedures) related costs for CIPII were estimated to be 30.901 Euros in the first year and 7.579 Euros in the following 6 years [84]. The annual costs of CIPII are estimated to be 6.000 Euros higher on average than CSII [84]. It should be noticed however that none of these costs-effectiveness analyses took into account the influence of CIPII on the hospital duration, which is reported to decrease from 45 days in the year before implantation to 13 days in the year after implantation [67]. At present, the costs of the MIP 2007D implantable pump are approximately 34.000 Euros and an ampoule of insulin (approximately 2 ampoules are needed per 6-week refill procedure) costs 500 Euros.

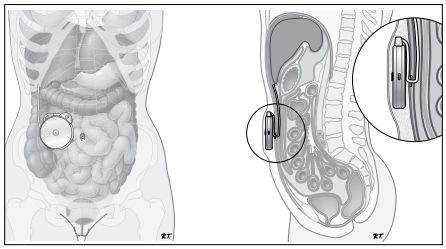
CURRENT USE OF CIPII

Due to limited evidence, risk of complications and high costs on the one hand and the further development of alternatives (e.g. glucose sensor-augmented pump therapy) on the other hand, CIPII is currently used only in a small number of T1DM patients. The current indications for CIPII therapy are based on data from available studies, that demonstrated benefits of the use of CIPII on glucose control in selected groups of patients, including: patients with documented SC defects of insulin absorption (e.g. due to skin reactions due to SC insulin administration, allergies, lipohypertrophy and/or lipoatrophy or SC insulin resistance), patients with recurrent bouts of severe hypoglycaemia (especially combined with hypoglycaemia unawareness) and patients showing sustained poor glucose control (HbA1c >58 mmol/mol (7.5%)) despite intensive SC insulin therapy that results in recurrent hospitalizations, very poor QoL and advanced diabetes complications [58,61,84–87]. Still, it should be acknowledged, that more evidence supporting these indications is needed.

The use of CIPII is largely restricted to Europe, especially Belgium, France, Sweden and the Netherlands. Besides the externally placed DiaPort system there is only one type of implantable pump (MIP 2007D, Medtronic/Minimed, Northridge, CA, USA) available for use in patients. This model has a reservoir which can contain 15 ml of insulin and has a battery with 7 years longevity. A silicone catheter is attached to the side port of the pump, through

FIGURE 3 The MIP 2007D implantable pump system and patients-pump communicator.

FIGURE 4 Illustration of the implantable pump system (left) and a the pump in situ (right) [83].



which insulin is delivered directly into the peritoneal cavity (see Figure 3 and 4). The pump can be remotely controlled with a pocket-sized personal pump communicator. Implantation of the pump is performed under general anaesthesia and, usually, the pump is inserted in a subcutaneous pocket in a lower abdominal quadrant (see Figure 4). From this pocket, the peritoneum is opened and the tip of the catheter is carefully inserted and directed towards the liver. After implantation, the pump reservoir is refilled transcutaneously with insulin at the outpatient clinic at least every 3 months, depending on the individual insulin requirement. From 2010 onwards a new human recombinant insulin (400 IU/ml; human insulin of E. Coli origin, trade name: Insuman Implantable®, Sanofi-Aventis) was used since no batches were left of the U-400 HOE 21PH insulin.

General aims and outline of this thesis

The general aim of this thesis was to study different aspects of CIPII using an implantable pump in patients with T1DM, in particular the effects of long-term use, in order to provide a more comprehensive and balanced view on the use of this therapy.

PART I. COMPLICATIONS OF CIPII THERAPY USING AN IMPLANTABLE PUMP

Chapter 2 focusses on the complications related to CIPII therapy. As complications occurred frequently in the past and influence the outcomes of CIPII therapy, it is of importance to monitor the course of complications related to CIPII. In this chapter the nature, consequences and course of complications of CIPII among patients with T1DM are described.

PART II. EFFECTS OF INTRAPERITONEAL INSULIN THERAPY - GLYCAEMIA, QUALITY OF LIFE AND TREATMENT SATISFACTION

Chapter 3 describes the long-term course of glycaemic regulation, general QoL and treatment satisfaction among CIPII treated patients. All patients described in this chapter initiated CIPII therapy during a cross-over trial in 2006, which allowed additional comparisons with both the initial effects of CIPII insulin and previous SC insulin therapy.
In *Chapter 4* the long-term effects of CIPII and SC insulin administration among T1DM patients with inadequate glycaemic control are described. Outcomes included the change of glycaemic control, clinical parameters and QoL within and between the two groups over a period of 7 years. In order to compare patients on long-term CIPII with a matched group of patients using SC insulin therapy, a 26-week prospective cohort study in a large population of T1DM patients was performed. *Chapter 5, 6 and 7* describe the results of this study with respect to glycaemic control and clinical parameters, glycaemic variability, general and diabetes specific QoL, treatment satisfaction, self-care and distress.

PART III. EFFECTS OF INTRAPERITONEAL INSULIN THERAPY - BEYOND GLYCAEMIA

In *Chapter 8* the hypothesis that the IP route of insulin administration would increase IGF1 concentrations as compared to SC insulin was tested using samples derived from a previous cross-over trial comparing SC and IP insulin therapy. *Chapter 9* describes the course of IGF1 concentrations after this cross-over trial, over a period of 6 years during CIPII therapy. Further testing and reporting on the effects of IP insulin, as compared to SC insulin administration, on the GH-IGF1 axis is performed in *Chapter 10*. As most studies towards this topic had a relative short duration and were performed in small populations, the effects of CIPII as compared to SC insulin administration on the GH-IGF1 axis were studied in a large population of T1DM patients who have been on their current mode of therapy for more than 4 years.

Finally, in *Chapter 11* (*Chapter 12* in Dutch) a summary of this thesis is given, together with a discussion of the results, recommendations for the clinical practice and future research directions.

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PART I

Complications of CIPII therapy using an implantable pump

CHAPTER 2 Complications of continuous intraperitoneal insulin infusion with an implantable pump in type 1 diabetes